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Proposal for a revised Reference Concentration (RfC) for manganese based on recent epidemiological studies

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ABSTRACT

In 1993, based on observations of subclinical neurological effects in workers, the United States Environmental Protection Agency (US EPA) published a Reference Concentration (RfC) of 0.05 μg/m^3 for manganese (Mn). The geometric mean exposure concentration, 150 μg/m^3 respirable Mn, was considered the lowest observable adverse effect level (LOAEL), and uncertainty factors (UFs) were applied to account for sensitive populations, database limitations, a LOAEL, subchronic exposure, and potential differences in toxicity of different forms of Mn. Based on a review of more recent literature, we propose two alternate Mn RfCs. Of 12 more recent occupational studies of eight cohorts with chronic exposure durations, examining subclinical neurobehavioral effects, predominantly on the motor system, three were considered appropriate for development of an RfC. All three studies yielded no observable adverse effect levels (NOAELs) of approximately 60 μg/m^3 respirable Mn. Converting the occupational NOAEL to a human equivalent concentration (HEC) of 21 μg/m^3 (for continuous exposure) and applying a UF of 10 to account for intraspecies variability yielded an RfC of 2 μg/m^3. We also derived a similar RfC (7 μg/m^3) using an Mn benchmark dose (BMD) as the point of departure. Overall confidence in both RfCs is medium.

1. Background

In 1993, the United States Environmental Protection Agency (US EPA) calculated a Reference Concentration (RfC) for Mn (US EPA, 2008) based on observations of subclinical neurological effects in workers exposed for an average of 5.3 years (Roels et al., 1992). Roels et al. (1992) examined visual reaction time, hand–eye coordination, hand steadiness, and audio-verbal short-term memory in 92 Mn-exposed dry alkaline battery workers and 101 unexposed polymer processing factory workers in Belgium. Based on an 8-h time-weighted average (TWA), the geometric mean exposure in the battery workers, 150 μg/m^3 respirable Mn, was considered the lowest observable adverse effect level (LOAEL). US EPA calculated a human equivalent concentration LOAEL (LOAEL$_{[HEC]}$) of 50 μg/m^3, which accounted for differences in exposure duration between workers and the general population. US EPA applied a total uncertainty factor (UF) of 1000 to the LOAEL$_{[HEC]}$ to account for sensitive populations (UF = 10); use of a LOAEL instead of a NOAEL (UF = 10); and database limitations, subchronic exposure, and potential differences in the toxicity of different forms of Mn (UF = 10), resulting in an RfC of 0.05 μg/m^3.

The mean ambient air concentration of Mn in the US as a whole is 0.02 μg/m^3 and is approximately 0.04 μg/m^3 in urban areas. Concentrations in areas near industrial sources can range from 0.22 to 0.3 μg/m^3 (ATSDR, 2008). Some of these values exceed the present RfC of 0.05 μg/m^3, implying a potential risk. Thus, it is important to consider implications of more recent scientific understanding on the RfC. Since the original RfC was developed, additional relevant studies have been published. These include pharmacokinetic studies, developmental toxicology studies in animals, and epidemiology studies examining exposure to Mn dust and neurological effects, considered the most sensitive effects. Below we describe how these studies provide NOAEL values and revised UFs for calculating an Mn RfC.

2. Methods

We conducted a literature search in PubMed using the following search terms: "manganese AND (neuro* OR neurotox* OR neurology OR neurologic*)." We limited the human studies to those that:

- Were published after 1992;
- Examined and reported Mn dust[1] as the exposure of concern, from personal air monitoring data;
- Evaluated both an exposed and an unexposed population;

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[1] Studies of welding fume exposures were excluded because, from a toxicological perspective, welding fumes are potentially very different from particulate Mn.

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- Evaluated neurological effects in relation to ongoing exposures to Mn in air.

Animal studies were limited to developmental studies conducted after 1992. In addition, to supplement the PubMed results for animal developmental studies, we conducted a search of the Developmental and Reproductive Toxicology (DART) database using the following search terms: "manganese OR colloidal manganese."

Although human studies that measured total Mn in air were located, for the RfC calculation, we focused on studies that measured the respirable fraction of Mn. Respirable particles ($\leqslant$10 μm in diameter) are capable of penetrating the lung tissue, while larger particles are trapped in the nasal and pharyngeal passages, do not penetrate the lung tissue, and do not enter the circulation (Klaassen, 2001). We recognize that, based on studies in rats, there has been some discussion as to the possibility of transport of nasally deposited Mn through the olfactory nerve to the brain (Henriksson and Tjalve, 2000; Vitarella et al., 2000; Brenneman et al., 2000; Dorman et al., 2002; Elder et al., 2006). However, we believe that this is an unlikely pathway in humans because of the considerable differences in the nasal and brain anatomy and physiology of rats and humans. As pointed out by Dorman et al. (2002), in the rat, the olfactory bulb accounts for a relatively large portion of the central nervous system. The olfactory mucosa represents about 50% of the total nasal epithelium in rats, as compared to only 5% of the human nasal epithelium. These differences suggest that the olfactory pathway in humans is likely to be less important as compared to rats. Moreover, as discussed by Dorman et al. (2002), there is compelling evidence to suggest that the striatum of the human brain is the primary target for Mn neurotoxicity, and not the olfactory bulb and tract. A recent pharmacokinetic study (Leavens et al., 2007) in rats predicted low transport efficiency for inhaled Mn from the olfactory pathway to the striatum, and the authors suggested that Mn could be transported *via* olfactory neurons in humans at the same rate as in rats.

We derived two Mn RfCs, following standard US EPA methodology (US EPA, 1994, 2002): one based on a NOAEL, and one based on the 95% lower confidence limit on a benchmark dose associated with 10% extra risk ($BMDL_{10}$)[2] derived by Clewell et al. (2003). We used arithmetic means of the concentrations for derivation of our NOAELs, based on studies suggesting that the arithmetic mean provides a better summarization of group exposure with regard to a dose–response relationship, and is therefore more appropriate for use in risk assessment (Clewell et al., 2003; Crump, 1998). However, if arithmetic means were not available, we used the geometric mean or median value.

3. Results

3.1. Derivation of a NOAEL from human studies

At least one study in eight cohorts met our initial criteria (i.e., published after 1992; examined and reported Mn dust as the exposure of concern, from personal air monitoring data; evaluated both an exposed and an unexposed population; and evaluated neurological effects in relation to ongoing exposures to Mn in air). Twelve studies from the eight cohorts, in addition to Roels et al. (1992), are summarized in Table 1, and are organized by cohort. All are occupational studies with chronic exposure durations (i.e., greater than seven years, based on 10% of a 70-year lifetime exposure). Observed effects, to the extent there were any, were subclinical neurobehavioral effects, predominantly on motor function (typically visual reaction time, hand–eye coordination, and hand steadiness). These eight cohorts are discussed below.

Several epidemiological studies were not included in our analysis because the exposure data were not individually based (i.e., no personal air monitoring data were collected), but rather reflected general air concentrations measured in residential populations (Santos-Burgoa et al., 2001; Rodriguez-Agudelo et al., 2006; Standridge et al., 2008) or occupational settings (Blond et al., 2007; Blond and Netterstrom, 2007). Because individual exposure concentrations are not known in these studies, the data are not as reliable as the occupational data we used here in derivation of toxicity values.

Three chronic studies of respirable Mn were identified from which NOAELs could be derived (Gibbs et al., 1999; Deschamps et al., 2001; Young et al., 2005). Gibbs et al. (1999) conducted a study of 75 Mn-exposed workers at an alkaline battery plant in northern Mississippi and 75 nearby plant workers with no known history of occupational exposure to Mn (73 were employed at a pigment-grade titanium dioxide plant and two were employed at the alkaline battery plant working in sodium chlorate production). The mean Mn air concentration in respirable dust in exposed workers was measured by personal air monitors to be 66 $\mu g/m^3$. The mean exposure duration was 12.7 years. Subjects were matched on sex, race, age, and salary and were administered multiple neuropsychological tests, including hand–eye coordination, hand steadiness, complex reaction time, and rapidity of motion. No significant effects of Mn exposure were found on any neurobehavioral test, resulting in a NOAEL of 66 $\mu g/m^3$.

Deschamps et al. (2001) conducted neurobehavioral examinations in 138 enamels-production workers exposed to Mn for an average of 19.9 years and 137 matched technicians from public service employers or local municipal operations laborers. Subjects were matched on age, education, and ethnic group. Based on personal monitor measurements, the mean respirable exposure concentration was 57 $\mu g/m^3$ and the maximum concentration was 293 $\mu g/m^3$ in exposed workers. No differences were found between mean concentrations of Mn in blood of exposed and unexposed workers. Tests conducted included sensory and motor exam of cranial nerves; fine-touch, motor, and sensory exam of power of all main muscle groups; reflex tests; cerebellar abnormalities; and tests of domains of speech regulation and initiation, attention, concentration and memory, cognitive flexibility, and affect; and a questionnaire for neuropsychological status. There was a higher prevalence of self-reported asthenia (lack of energy and strength), sleep disturbance, and headache in exposed workers. It is unclear whether these non-specific symptoms were exposure-related because the group of exposed subjects who previously expressed non-specific subjective symptoms had low levels of blood Mn. In addition, the visual gestalt test score was higher in workers exposed to Mn for 11–15 years, but the authors attribute this to the higher technical skills of this group of six workers. This is supported by a lack of dose–response relationship, as no statistically significant effects were noted in the four people exposed 16–19 years or the 69 people exposed for 20+ years. Based on these results, the authors concluded that "long exposure to low levels of Mn...showed no significant disturbance of neurological performance." Results of this study indicated a NOAEL of 57 $\mu g/m^3$.

Young et al. (2005) conducted a study of 509 South African Mn-exposed smelter workers and 67 unexposed electrical assembly plant workers. Respirable Mn exposures ranged from 3 to 510 $\mu g/m^3$, with a median of 58 $\mu g/m^3$. Exposure indices for individuals were attributed or interpolated from 98 personal samplers. The study authors assessed several neurobehavioral endpoints, including items from the Swedish nervous system questionnaire

[2] The term "BMD" is used here to be consistent with the terminology used by Clewell et al. (2003), although it is technically a Benchmark Concentration (BMC).

Table 1
Chronic manganese inhalation occupational studies published in or after 1992.

Reference	Location	Exposed population (*n*)	Non-exposed population (*n*)	Mean exposure duration (years)	Neurological tests employed	NOAEL ($\mu g/m^3$)	LOAEL ($\mu g/m^3$)	Findings statistically significantly associated with Mn
Study used as basis of current US EPA IRIS RfC								
Roels et al. (1992)	Belgium	Dry alkaline battery workers (92)	Polymer processing factory workers (101)	5.3	• Visual reaction time • Hand–eye coordination • Hand steadiness • Audio-verbal short-term memory	NA	Geometric mean respirable Mn: 150 (lifetime integrated exposure of 793 $\mu g/m^3$/5.3 years) Personal sampler	• Visual reaction time • Hand–eye coordination • Hand steadiness
Cohort 1								
Chia et al. (1993)	Singapore	Milling plant baggers (17)	Hospital housekeeping workers (17)	7.4	• Digit span • Santa Ana dexterity test • Digit symbol test • Benton visual retention test • Pursuit aiming test • Finger tapping • Trail making test	NA	Mean total Mn (95% CI): 1590 (1190–1990) Personal sampler	• Motor speed • Visual scanning • Visuomotor coordination • Visuomotor and response speed • Visuomotor coordination and steadiness
Cohort 2								
Mergler et al. (1994)	Quebec	Workers at ferro/silico manganese plant (115)	Workers from neighboring plants (145)	16.7	• Motor functions • Sensory functions • Speech initiation and regulation • Attention, concentration, and memory • Cognitive flexibility • Profile of mood states • Profile of mood states	NA	Arithmetic mean respirable Mn: 122 Personal and stationary samplers	• Emotional state • Motor functions • Cognitive flexibility • Olfactory perception threshold
Bouchard et al. (2006, 2007)	Follow-up of Mergler et al. (1994) cohort SW Quebec	Former workers from ferro/silico manganese plant (77)	Workers from neighboring plants (81)	15.7	• Neuropsychiatric symptoms (brief symptom inventory) • Global indices of distress • Neurobehavioral tests (Motor Scale of the Luria-Nebraska Neuropsychological Battery, finger tapping, dynamometer, Nine-Hole Hand Steadiness, Cancellation H, Trail Making A&B, Stroop color-word test, digit span, delayed word recall, symbol digit modalities test) • Profile of mood states	NA	Arithmetic mean respirable Mn: 122 Personal and stationary samplers	• Depression and anxiety • Poorer scores on the Luria Motor Scale, the Hand Steadiness Test, and the color-word trial of the Stroop Color-Word test as well as the Confusion-Bewilderment POMS scale
Cohort 3								
Gibbs et al. (1999)	Northern Mississippi	Alkaline battery plant workers with recent (63) and/or historical (12) exposure	Pigment-grade titanium dioxide plant workers (73) and sodium chlorate production facility workers (at alkaline battery plant) (2)	12.7	• Hand–eye coordination • Hand steadiness • Complex reaction time • Rapidity of motion • Steadiness • Tap time	Arithmetic mean (SD) respirable Mn: 66 (59) Personal sampler	NA	None
Cohort 4								

Lucchini et al. (1995)	Italy	Male workers from Italian ferro-alloy plant (58) during forced cessation of work (1–42 days). High exposure (19), medium exposure (19), low exposure (20)	None	13.8 (high) 11.8 (medium) 12.9 (low)	• Simple reaction time • Shapes comparison • Additions • Symbol digit • Finger tapping • Digit span	NA Personal and stationary samplers	Range of geometric means (over 10 years) total Mn: 270–1590 Personal and stationary samplers	• Additions • Symbol digit • Finger tapping • Digit span
Lucchini et al. (1999)	Follow-up of Lucchini et al. (1995)	Ferro-alloy male Workers (61)	Maintenance and auxiliary workers from a local hospital (87)	15.2	• Addition, digit span, finger tapping, symbol digit • Motor tasks (open–closed hand tests, thumb–finger touch tests) • Potural tremor • Coordination (hand protonation/supination, reaction time) • Symptoms	NA	Geometric mean total Mn: 97 μg/m3 (Geomean cumulative exposure index of 1113 μg/m^3 from mid-group/geomean of 11.51 years) Personal and stationary samplers	• Irritability, loss of equilibrium and rigidity • Symbol digit, finger tapping, and digit span tests
Cohort 5								
Crump and Rousseau (1999)[a]	Belgium	Manganese oxide workers (114)	Chemical plant (104)	14	• Short-term memory • Hand–eye coordination • Hand steadiness • Visual reaction time	NA	Median total Mn: 970[b] Personal sampler	None
Cohort 6								
Deschamps et al. (2001)	France	Enamels-production workers (138)	Technicians from public service employers and laborers from local municipal operations (137)	19.9	• Sensory and motor exam of cranial nerves • Fine-touch, motor, and sensory exam of power of all main muscle groups • Reflex test • Cerebellar abnormalities • Tests of domains of speech regulation and initiation, attention, concentration, and memory, cognitive flexibility, and affect • Questionnaire for neuropsychological status	Arithmetic mean (SD) respirable Mn: 57 (84) Personal sampler	NA	The visual gestalt test score was higher in workers exposed to Mn for 11–15 years, but the authors attribute this to the higher technical skills of this group of six workers. This is supported by a lack of dose–response relationship, as no statistically significant effects were noted in the four people exposed 16–19 years or the 69 people exposed for 20+ years
Cohort 7								
Bast-Pettersen et al. (2004)	Not stated	Mn alloy plant workers (100)	Silicon and microsilica plant and titanium dioxide slag and pig iron plant workers (100)	20.2	• Cognitive functions (Wechslers adult intelligence scale, digit symbol, trail making test, Stroop test) • Motor tests (hand steadiness/ tremor/Klove–Matthews static readiness test, TREMOR test) • Motor speed/grip strength (finger tapping, foot tapping, dynamometer, grooved pegboard, CATSYS, Luria-Nebraska thumb–finger touch, simple reaction time, hand–eye coordination)	NA	Arithmetic mean (range) respirable Mn: 64 (3–356) Personal sampler	• Postural tremor in visually guided tremor tests • Increased duration of contacts • Larger frequency dispersion of tremor • Tremor increased in exposed smokers vs. non-smokers

(*continued on next page*)

Table 1 (*continued*)

Reference	Location	Exposed population (*n*)	Non-exposed population (*n*)	Mean exposure duration (years)	Neurological tests employed	NOAEL ($\mu g/m^3$)	LOAEL ($\mu g/m^3$)	Findings statistically significantly associated with Mn
Cohort 8 Young et al. (2005) *Note:* Myers et al. (2003) observed similar results in the same cohort based on total manganese concentrations	South Africa	Manganese smelter workers (509)	Electrical assembly plant workers (67)	18.2	• Digit span (forward and backward), digit symbol, Santa Ana • Mean reaction time, tapping dominant and non-dominant hand, endurance • Catsys, tremor, and sway • Luria-Nebraska test	Median (range) respirable Mn: 58 (3–510) Exposure indices attributed or interpolated from 98 personal samplers	NA	Statistically significant associations observed for almost all neurological tests. These occurred primarily with concentrations <100 $\mu g/m^3$, above which the relationships were "flat." Thus, these effects are likely not to be treatment-related

NA, not applicable.
[a] Study of the same cohort of Mn-oxide salt workers as that in Roels et al. (1987).
[b] From Roels et al. (1987), as presented in IRIS.

(Q16), the World Health Organization neurobehavioral core test battery (WHO NCTB), the Swedish performance evaluation system (SPES), the Luria-Nebraska (LN), the Danish Product Development (DPD) test batteries, and a brief clinical examination. The study found "few respirable Mn effects showing a clear continuity of response with increasing exposure." They observed dose–response associations primarily with exposures less than 100 $\mu g/m^3$, above which the relationship was flat. The authors concluded that the study was essentially negative and that "the small number of convincing effects, especially motor function effects, and the character of the exposure–response relationships where effects were observed in this study suggests that these are due to chance." Although these data are less reliable than those reported in the Gibbs et al. (1999) and Deschamps et al. (2001) studies, a NOAEL of 58 $\mu g/m^3$ is assumed based on the likelihood of positive findings being due to chance.

Six studies evaluated total, rather than respirable, Mn (Chia et al., 1993; Lucchini et al., 1995, 1999; Crump and Rousseau, 1999; Myers et al., 2003), and thus were not considered further for calculating the RfC. Myers et al. (2003) evaluated the same cohort as Young et al. (2005), but examined total, rather than respirable Mn concentrations, and found similar results. It should be noted that the LOAELs in these studies ranged from 96 to 1590 $\mu g/m^3$.

Mergler et al. (1994) evaluated neurological effects of 74 Mn alloy workers and 74 matched controls exposed for an average of 16.7 years to a wide range of respirable Mn air concentrations (ranging from 1 to 1273 $\mu g/m^3$), with an arithmetic mean of 122 $\mu g/m^3$. The authors evaluated the Mn-exposed workers only as a whole (over the full range of exposure concentrations), and found that the exposed workers performed more poorly on tests of motor function. This study yielded a LOAEL of 122 $\mu g/m^3$ as an arithmetic mean. Because of the wide range of exposure concentrations in this group, we concluded that this study would not provide a reliable basis, as compared to the selected studies, for development of an RfC. Bouchard et al. (2006, 2007) were follow-up studies of the same cohort after cessation of exposure.

Finally, in a study by Bast-Pettersen et al. (2004), a large number of neuropsychological tests were carried out on 100 Mn alloy plant workers and 100 silicon and microsilica plant and titanium dioxide slag and pig iron plant workers, including tests for cognitive functions; motor tests; tests of motor speed, grip strength, coordination, and reaction time; and a questionnaire to evaluate self-reported neuropsychiatric symptoms. Average exposures were 64 $\mu g/m^3$ (range: 3–356 $\mu g/m^3$). Of the tests, only three of eight motor tests (tremor tests) showed significant effects in the exposed vs. the control group. The cognitive tests and other neuropsychological tests were not significantly different in the exposed vs. the control group, and there was also no significant difference in self-reported neuropsychiatric symptoms between the two groups. Self-reported smoking habits had an effect on tremor parameters. The lack of consistency among the tremor tests suggests that these findings are not robust for determining an RfC.

Thus, the three most appropriate studies for developing an RfC are those by Gibbs et al. (1999) (NOAEL = 66 $\mu g/m^3$), Deschamps et al. (2001) (NOAEL = 57 $\mu g/m^3$), and Young et al. (2005) (NOAEL = 58 $\mu g/m^3$). Because these NOAELs are all very close to 60 $\mu g/m^3$, we chose 60 $\mu g/m^3$ as the point of departure for derivation of an Mn RfC.

3.1.1. *Clewell et al. (2003) benchmark dose calculation*

A benchmark dose (BMD) is the dose or concentration of a substance inhaled that is associated with a specified low incidence of risk, generally in the range of 1–10%, of a health effect; or the concentration associated with a specified measure or change of a biological effect. The BMDL is the lower one-sided confidence limit

on the BMD. The BMDL approach is generally preferable to the NOAEL/LOAEL approach (US EPA, 2000). Typically, the limitation to using a NOAEL (or LOAEL) approach is that it is constrained to one of the experimental concentrations within the exposed group (Crump, 1984; Barnes et al., 1995; Gaylor et al., 1998). Since we did not have the underlying data for the three studies from which we derived a NOAEL (Gibbs et al., 1999; Deschamps et al., 2001; and Young et al., 2005), we did not calculate a manganese BMD from those studies. However, as described above for derivation of the Mn NOAEL, the three studies support very similar NOAELs, providing more support for the NOAEL approach in derivation of the Mn RfC. In addition, here we describe BMDL calculations carried out by Clewell et al. (2003), one of which was based on data from Gibbs et al. (1999) used in our analysis. We used the Clewell et al. (2003) BMDL as the point of departure of another Mn RfC that we derived, providing a range of possible RfCs based on both NOAELs and BMDLs.

Clewell et al. (2003) obtained individual exposure and response information from the authors of the Roels et al. (1992) study, on which the current RfC is based, and the Gibbs et al. (1999) study, which is discussed above. The data provided from the Roels et al. (1992) study were discrete (i.e., either normal or abnormal response), so Clewell et al. (2003) modeled visual reaction time, hand–eye coordination, and hand steadiness using the Weibull model for quantal data. Continuous data were provided for the Gibbs et al. (1999) study, so Clewell et al. (2003) modeled each endpoint [hand steadiness, hand–eye coordination, reaction time, steadiness (RMS amplitude), and tap time] using the discrete or continuous data Weibull model or the k-power model. For the eight endpoints from these studies, Clewell et al. (2003) derived BMDs on the order of 300 $\mu g/m^3$, and $BMDL_{10}$ values ranged from 90 to 270 $\mu g/m^3$, with a mean of 200 $\mu g/m^3$.

Clewell et al. (2003) suggested that (1) BMDLs obtained from analyses using continuous data that had been redefined as quantal result in a loss of information and lower BMDLs; (2) BMDLs from the Gibbs et al. (1999) study are likely to be highly conservative since none of the endpoints were statistically significantly correlated with the Mn exposure variable; (3) the subtle, subclinical effects represented by the neurological endpoints measured in both studies do not meet the definition of material impairment used by the Occupational Safety and Health Administration (OSHA). Therefore, it is appropriate to apply the average $BMDL_{10}$, 200 $\mu g/m^3$, derived by Clewell et al. (2003) as an alternate point of departure for an additional Mn RfC.

3.1.2. Uncertainty factors

Several recent studies have allowed for a re-evaluation of the UFs used for calculating the Mn RfC. These studies bear on the use of UFs for subchronic studies, a LOAEL study, intraspecies variation, and a lack of developmental data. The respirable Mn studies by Gibbs et al. (1999), Deschamps et al. (2001), and Young et al. (2005) all identified a NOAEL. They can also each be considered a chronic study because exposures occurred for greater than seven years: 12.7 years (Gibbs et al., 1999); 19.9 years (Deschamps et al., 2001); 18.2 years (Young et al., 2005) (also see discussion in Section 3.1.2.4). Therefore, use of these studies eliminates the need for subchronic and LOAEL UFs. In addition, although the Roels et al. (1992) subchronic study was one study used by Clewell et al. (2003) to derive the BMDL, as described below, use of this study did not require a subchronic UF.

3.1.2.1. Intraspecies UF. There have been recent advances in the understanding of the pharmacokinetics of inhaled Mn in potentially sensitive individuals. This has been extensively studied (Dorman et al., 2004, 2005a,b, 2006a) and reviewed by Dorman et al. (2006b); these authors compared the Mn brain concentrations of healthy young adult male rats to rats that were considered to reflect potentially susceptible sub-populations (aged; abnormal hepatobiliary function; sub-optimal iron or Mn intake; and fetuses, neonates, and children). The authors concluded that inhaled Mn particles result in "qualitatively similar end-of-exposure brain Mn concentrations" in the potentially susceptible sub-populations as compared to healthy young adult male rats. They further concluded that, based on the studies reviewed, a "UF of 3 to account for intraspecies variations in Mn pharmacokinetics may be sufficient to protect potentially susceptible sub-populations." These studies suggest that a UF of 3 for pharmacokinetic differences is sufficient. Applying an additional UF of 3 for pharmacodynamic differences results in a UF of 10 for intraspecies variability. More recently, physiologically based pharmacokinetic (PBPK) models for Mn have been developed (Teeguarden et al., 2007a,b,c; Nong et al., 2008, 2009), which provide a thorough quantitative analysis of the UF for intraspecies variability.

In addition, based on the Dorman studies (Dorman et al., 2004, 2005a, 2006a), the Manganese Interest Group (MIG) (Environ, 2008; Green, 2008) has proposed an accumulation threshold for Mn in brain tissue. These investigators used non-linear regression modeling of the Dorman data (Green, 2008) as support for Mn accumulation beginning in brains of neonatal rats, adult rats, and primates at concentrations greater than or equal to 10 $\mu g/m^3$.[3] An accumulation threshold for Mn is biologically plausible because Mn is an essential nutrient, and homeostatic control mechanisms limit accumulation of essential nutrients at doses less than an accumulation threshold (Santamaria, 2008).

Mn pharmacokinetic models currently being developed (Teeguarden et al., 2007a,b,c; Nong et al., 2008, 2009) should help in application of the kinetic data to humans. As further analyses are published, the implications for the intraspecies UF and for a threshold for Mn accumulation will need to be examined. To the extent that exposures do not exceed the accumulation threshold and, assuming the accumulation threshold is similar across sub-populations, the need for the intraspecies UF may be obviated. In any case, our proposed RfCs (2 $\mu g/m^3$ based on the NOAEL and 7 $\mu g/m^3$ based on the BMDL, shown in calculations below) are below the proposed threshold.

3.1.2.2. UF for developmental effects. Since 1993, several Mn inhalation studies have been conducted in animals to address the potential for developmental effects (Dorman et al., 2005a,b; Erikson et al., 2005; HaMai et al., 2006; Rindernecht et al., 2005). (It should be noted that the Rindernecht et al., 2005 analysis is a meeting abstract. We include it here for completeness, but the study should be considered preliminary until the findings are formally published.) In the developmental studies, the lowest concentration where an effect was observed was 500 $\mu g/m^3$ (Dorman et al., 2005a). At this concentration, decreased liver weights were observed only in male offspring and only at post-natal day (PND) 63. Liver weights at the high dose (1 mg/m^3) were not decreased at this time point, although they were decreased on PND 19. Given that the decrease in liver weight does not appear to be dose-dependent and resolves at the highest dose by PND 45, this endpoint is of questionable significance and may not even be treatment-related. Two of the studies resulted in a LOAEL of 700 $\mu g/m^3$, based on alterations in brain development and susceptibility to brain injury in rats after *in utero* exposure (poster abstract by Rindernecht et al. (2005)), and decreased expression of inflammation-related genes in the brains of rats exposed during gestation or early adulthood (HaMai et al.,

[3] The MIG proposal for an accumulation threshold for Mn in brain tissue can be found in its comments on the Health Canada "Draft Human Health Risk Assessment for Inhaled Manganese," available from Health Canada upon request (Health Canada, 2008).

2006). The other Dorman study (Dorman et al., 2005b) resulted in a NOAEL of 1 mg/m^3 based on a lack of clinical fetotoxicity in rats at this dose. Erikson et al. (2005) exposed neonatal rats to 0.05, 0.5, or 1 mg $MnSO_4$/m^3 during gestation through PND 18 (except for the period when parturition was expected to occur). Three weeks post-exposure, rats were sacrificed and metallothionein and glutamine synthetase mRNA levels and glutamine synthetase and glutathione protein levels were measured in five brain regions. While changes were observed at some doses in some brain regions for all measured endpoints, the findings did not always exhibit a dose–response and were not always consistent in males in females. In any case, the changes in mRNA and protein transcription at the lowest dose level (0.05 mg/m^3) are not appropriate for identification of a LOAEL. The RfC, by definition, is based on a critical effect that considers adverseness, and may result in functional or structural impairment or be a precursor state to irreversible toxicity (US EPA, 1990). US EPA defines the "critical effect" as "the first adverse effect, or its known precursor, that occurs to the most sensitive species as the dose rate of an agent increases" (US EPA, 2002). Therefore, the selected effect should be a critical effect on a causal pathway to disease. In determination of a critical effect, it is important that distinctions be realized between adverse and adaptive effects; adaptive effects may enhance an organism's performance, whereas an adverse effect impairs performance (Strawson et al., 2004; Barnes and Dourson, 1988). In the case of changes in mRNA or protein synthesis, the toxicological significance of these changes is unknown. It is possible that with such sub-cellular events, adaptive responses at higher levels of biological organization may result in homeostasis (Conolly, 2009). Thus, the LOAEL of 500 μg/m^3 (translated to a NOAEL of 50 μg/m^3) from the Dorman et al. (2005a) study, based on decreased liver weight, remains the appropriate value for comparison to the neurological effects NOAEL.

The developmental NOAEL of 50 μg/m^3 is approximately equal to the NOAEL for human neurological effects (Table 1). Converting this rodent NOAEL of 50 μg/m^3 into a $NOAEL_{[HEC]}$[4] yields a value of 32 μg/m^3, which is higher (i.e., less restrictive) than the $NOAEL_{[HEC]}$ of 21 μg/m^3 calculated from neurological effects (see discussion in section below). In addition, the UF for intraspecies variability, to an extent, already addresses potential developmental effects. That is, Dorman and coworkers (Dorman et al., 2006b, 2005b) observed that a threefold UF for pharmacokinetic differences was adequately protective across life stages, noting that, at Mn concentrations of 0.05, 0.5, and 1 μg/m^3 Mn, fetal and neonatal Mn brain concentrations were not very different from adult brain concentrations. These studies provide sufficient evidence to suggest that developmental effects from inhalation of Mn are not more sensitive than neurological effects. Therefore, a UF for developmental effects is not necessary.

3.1.2.3. UF for Mn species differences in toxicity. Dorman et al. (2006b) stated that Mn brain concentrations reflect Mn species solubility, with the more soluble forms of Mn leading to higher tissue concentrations. The solubility of Mn species is generally: soluble sulfates > less soluble phosphates > oxides (Dorman et al., 2006b). According to the European World Health Organization's Manganese Air Quality Guidelines (WHO, 2001), the most common forms of Mn compounds are oxides or hydroxides, and the Mn emitted by metallurgical processes consists of Mn oxides. Metallurgical processes include the use of metallic Mn (ferromanganese) in steel production (ATSDR, 2008). According to the Agency for Toxic Substances and Disease Registry (ATSDR, 2008), the majority of Mn ore consumed in the US is associated with steel production. Mn dioxide is also commonly used in production of dry-cell batteries, matches, fireworks, porcelain and glass-bonding materials, amethyst glass, and as the starting material for production of other Mn compounds (ATSDR, 2008). Therefore, the oxides are likely the most common Mn species to which people are exposed. Moreover, the exposures in the epidemiological studies used to derive our proposed RfCs were to the most common form of Mn–Mn oxides [alkaline battery production (Roels et al., 1992); electrolytic Mn (Gibbs et al., 1999); ferromanganese smelting (Young et al., 2005)]. Thus, application of a UF of 10 for Mn species differences is not necessary for an RfC that will be applicable in the majority of cases within the general population. Adjustment of the RfC to account for potentially more soluble, more bioavailable, and potentially more toxic forms of Mn, such as Mn sulfates, should be considered only on an exposure-specific basis. It may be appropriate to consider two RfCs, one for less soluble forms (oxides) that are likely the most common forms people are exposed to, and one that could be used for exposure to more soluble forms of Mn. Or, if a UF is applied to account for differences in toxicity of Mn species, an adjustment should be allowed for exposures to the less bioavailable (more common) Mn species.

3.1.2.4. UF for a subchronic study. Although the subchronic Roels et al. (1992) study was one of the studies used by Clewell et al. (2003) to derive the BMDL, a UF for use of a subchronic study is not necessary. As described in Clewell et al. (2003), analysis of the dose response data for subclinical effects of Mn provides evidence that exposure concentration and duration are the determining factors for the appearance of subclinical effects. In particular, the authors evaluated the Roels et al. (1992) data and found that the duration of occupational exposure was not significantly correlated to any measure of psychomotor response. In addition, as noted by Clewell, based on the BMDL derivation, although the average duration of Mn exposure was three times greater in the Gibbs et al. (1999) study than in the Roels et al. (1992) study (14.1 years vs. 5.7 years), the BMDLs based on current exposure concentration calculated from these studies were comparable. Thus Clewell et al. (2003) concluded that because the effects measured in these studies do not appear to depend on exposure duration, an adjustment downward for potentially longer exposure durations is not necessary.

3.1.3. RfC calculations

The Mn RfC was calculated by first converting the NOAEL and BMDL to a $NOAEL_{[HEC]}$ and $BMDL_{[HEC]}$ by converting the human occupational exposure to a continuous exposure for the general population (US EPA, 2009). That is:

$$\begin{aligned} NOAEL_{[HEC]} &= NOAEL \times 5/7 \text{ days} \times 10/20 \text{ m}^3/\text{day} \\ BMDL_{[HEC]} &= BMDL \times 5/7 \text{ days} \times 10/20 \text{ m}^3/\text{day} \end{aligned} \quad (1)$$

Using the NOAEL of 60 μg/m^3 derived from the studies reviewed here results in $NOAEL_{[HEC]}$ = 60 μg/m^3 × 5/7 days × 10/20 m^3/day = 21 μg/m^3. Similarly, using the $BMDL_{10}$ of 200 μg/m^3 derived by Clewell et al. (2003) results in a $BMDL_{[HEC]}$ of 71 μg/m^3.

The RfC can then be calculated in the following manner:

$$RfC = NOAEL_{[HEC]} \text{ or } BMDL_{10[HEC]}/UFs \quad (2)$$

Applying a UF of 10 for intraspecies variability leads to an RfC of 2 μg/m^3 (21 μg/m^3/10) from the NOAEL and 7 μg/m^3 (71 μg/m^3/10) from the $BMDL_{10}$.

3.1.4. Confidence in the RfC

Confidence in our RfCs was determined based on US EPA guidelines (US EPA, 1994), and is:

[4] The $NOAEL_{[HEC]}$ was calculated using the following assumptions: the geometric mean diameter was 1.03 μm, with a geometric standard deviation of 1.52. Sprague–Dawley rats were assumed to weigh 204 mg. The experiment exposures were adjusted to reflect 24-h, 7 days/week exposure (US EPA, 1994).

- HIGH for studies;
- MEDIUM for database;
- MEDIUM for RfC.

Confidence in the principal studies (Gibbs et al., 1999; Deschamps et al., 2001; Young et al., 2005) is high. All studies measured respirable concentrations of Mn, and tested similar neurological endpoints (e.g., visual reaction time, hand–eye coordination, and hand steadiness). The exposure information was well-characterized and similar across studies (i.e., large and closely matched control and exposed populations, chronic exposure durations, use of personal air monitoring samplers to estimate exposure concentrations, and exposure concentrations remained fairly consistent over the exposure period). And all three studies examined low enough concentrations to report a NOAEL. The NOAELs from all three studies were very similar (approximately 60 μg/m^3), which adds more support to the individual NOAELs. Confidence in the Roels et al. (1992) study is also high for the same reasons discussed for the other studies, except that Roels et al. (1992) did not identify a NOAEL. However, a $BMDL_{10}$ was derived by Clewell et al. (2003) from the Roels et al. (1992) study, eliminating the need for a NOAEL, and forming the basis of one of our RfCs. In addition, Clewell et al. (2003) derived a similar $BMDL_{10}$ value from the Gibbs et al. (1999) study. The $BMDL_{10}$ values (200 μg/m^3) derived by Clewell et al. (2003) were very similar to the NOAELs (60 μg/m^3) derived here. Therefore, four well-conducted occupational studies resulted in very similar points of departure.

Confidence in the database is medium. The essentiality of Mn is not well understood in the context of inhaled Mn, but as more pharmacokinetic data become available, implications for a threshold for Mn accumulation will need to be examined. Additional developmental and reproductive studies, particularly in humans, would add more confidence to the database; however, current pharmacokinetic data (Dorman et al., 2005b, 2006b) indicate that fetal and neonatal brain concentrations are not very different from maternal brain concentrations, and current developmental effects studies described here suggest that the developmental endpoint is not more sensitive than the neurological endpoint. The occupational studies also do not address the older population. However, a study in older rats (Dorman et al., 2004) has shown that age did not affect delivery of Mn to the striatum, a known target for neurotoxicity in humans. Overall, the UF for intraspecies is based, in part, on pharmacokinetic data for the various sub-populations (including the aged, fetal, and neonatal sub-populations) that suggest Mn brain concentrations do not vary more than threefold.

According to US EPA guidelines (1994), high confidence in the principal studies and medium confidence in the database results in medium confidence in the inhalation RfC.

4. Discussion

Based on recent studies in the peer-reviewed scientific literature, US EPA's current Mn RfC of 0.05 μg/m^3 is outdated and a reassessment is in order. Our assessment suggests a revised Mn RfC of 2–7 μg/m^3.

Findings from ongoing research and modeling studies should be considered in the context of our proposed RfC, although we believe it is unlikely that this information would lead to a more restrictive value. Specifically, PBPK models may provide for a pharmacokinetically based intraspecies UF, but the underlying data support a value no greater than threefold for intraspecies pharmacokinetic differences. Improved understanding of Mn essentiality and homeostatic mechanisms may help more precisely identify an accumulation threshold, but the available data suggest that this threshold is well above our proposed RfC.

Although some agencies have applied a UF for developmental effects (see below), compelling reasons indicate that such an adjustment is not necessary. For example, as shown by Dorman et al. (2005b), fetal rat brain concentrations were not affected by maternal exposure to inhaled Mn concentrations as high as 1 mg/m^3, suggesting that the placenta may sequester Mn, limiting delivery of Mn to the fetal brain. The study also showed that the neonatal Mn concentrations were only two- to three-fold higher than maternal brain concentrations. And as discussed in Dorman et al. (2006b), this increase may reflect an increased need for Mn in the developing neonate. In addition, the Dorman et al. (2005b) study, along with studies of other potentially susceptible sub-populations, formed the basis of the UF of 10 for intraspecies variability (UF of 3 for pharmacokinetic and 3 for pharmacodynamic differences). Therefore, the intraspecies UF already addresses potential developmental effects.

Several agencies have recently proposed DRAFT Mn inhalation toxicity criteria. These values and their bases are summarized in Table 2.

Both the ATSDR and California EPA point of departure values are very similar to those used in our analysis. Health Canada's point of departure is lower, but could be the result of a potential low bias in the Lucchini et al. (1999) data set. The reason for the potential bias is that substantial improvement of the ventilation system in 1988–1989 (as noted by the study authors) resulted in decreases in Mn concentrations from 1981 to 1995. Moreover, the monitoring data from the Lucchini et al. (1999) study are only from a small time period compared to the exposure period evaluated (15.7 years); survey data were available from 1981, but annual monitoring did not take place until 1988. Therefore, the exposure data between 1981 and 1988 are uncertain and exposures from this time period could be underestimated, since they occurred prior to installation of the ventilation system. In

Table 2
Recent DRAFT Mn inhalation toxicity criteria.

Agency	Exposure period	Point of departure × HEC conversion[a]	Uncertainty factors	Value
ATSDR (2008)	Chronic Minimal Risk Level (MRL)	142 μg/m^3 $BMCL_{10}$ × 5/7 days × 8/24 h/day (Roels et al., 1992)	10 (intraspecies) 10 (database limitations: Mn species; sensitivity to children) 100 (total)	0.3 μg/m^3
Health Canada (2008)	Chronic RfC	19.2 μg/m^3 $BMCL_{05}$ × 5/7 days × 8/24 h/day (Lucchini et al., 1999)	10 (intraspecies) 10 (database limitations: Mn species; sensitivity to children) 100 (total)	0.05 μg/m^3
California EPA (2008)	Chronic Reference Exposure Level (REL)	72 μg/m^3 $BMCL_{05}$ × 5/7 days × 10/20 m^3/day (Roels et al., 1992)	3 (subchronic study) 100 (intraspecies: 10 for toxicokinetic and 10 for toxicodynamic differences) 300 (total)	0.09 μg/m^3

[a] HEC conversion was determined by the Agency.

addition, the Health Canada value uses a 95% lower confidence limit on a benchmark concentration (same as benchmark dose, but used for concentrations in air) associated with 5% extra risk ($BMCL_{05}$), rather than the more conventional $BMCL_{10}$ (10% extra risk) recommended by US EPA (2000). All three agencies incorporate UFs to account for early life exposures. As discussed, a UF of 10 for intraspecies variability already addresses developmental effects. ATSDR and Health Canada apply a UF to account for differences in toxicity for different Mn species. A toxicity value based on the more common environmental form of Mn (i.e., the less soluble Mn oxides) would be more generally applicable. If an RfC incorporates a UF to account for more soluble forms of Mn, adjustments must be allowed, on a case by case basis, to adjust the exposure for less soluble forms of Mn.

Uncertainties in application of the epidemiology studies described are likely to be low, as discussed in meta-analyses by Lees-Haley et al. (2006) and Greiffenstein and Lees-Haley (2007). Specific neuropsychological tasks, preclinical neurological indicators, biological body burden, subject demographic variables, and dose–response correlations were analyzed in a recent meta-analysis of 19 occupational studies (Greiffenstein and Lees-Haley, 2007). The authors concluded, "The data did not support a theory of preclinical ("early") neuromotor or cognitive dysfunction. Overall, the pooled data are more consistent with covariate effect than toxic effect, insofar as the pooled exposure group showed demographics less favorable to neuropsychological performance than the pooled referent groups." An earlier meta-analysis (Lees-Haley et al., 2006) reviewed 20 occupational studies to determine the effects of occupational exposure to Mn on neuropsychological functioning. The authors concluded that "occupational exposure to Mn, at levels that are typically seen around the world, does have a small deleterious effect on cognitive and sensory motor performance. An effect of this magnitude is detectable in population studies; however, it is generally too small to be detected in any one individual through current clinical assessment, so it is not clear that such an effect has any clinical significance."

In contrast, Meyer-Baron et al. (2009) conducted a meta-analysis of several of the studies reviewed here and concluded, "Apart from two outcomes, the overall effects displayed a negative impact of manganese on performance." This study focused on total Mn (vs. respirable Mn) and excluded several relevant studies for various reasons (e.g., mean and standard deviation of performance were not reported). The investigators used linear meta-regression models to evaluate several endpoints. Fig. 1 of Meyer-Baron et al. (2009), which shows digit symbol and finger tapping data, indicates that a non-linear threshold model is likely to be more appropriate than the linear model used by the authors. In addition, the authors stated that the low end of the range of concentrations where they said effects were observed is consistent with the low end of the effects range (0.05 mg/m^3) described by Lucchini et al. (1999). However, 0.05 mg/m^3 is the "overall" concentration in the Lucchini et al. (1999) study, within which the authors derive a LOAEL for total Mn of 0.097 mg/m^3 (as noted in our Table 1), based on the mid-level exposed group.

The lack of clinical significance is important to consider in deriving the RfC. The purpose of the RfC is to protect against *adverse* health effects. If the subclinical neurological effects observed in the Mn occupational studies used to derive the RfC have no clinical significance, then the RfC is conservative. Another uncertainty regarding the application of the epidemiology data includes the use of the arithmetic mean of respirable Mn for each exposed subject. In most of these studies, there was a wide range of exposures, often over orders of magnitude, leading to the derivation of NOAELs and LOAELs with much variability. Analyses using the $BMDL_{10}$ were based on individual data, however, and are not subject to this limitation. Because results using the NOAEL and using the $BMDL_{10}$ were similar, it is unlikely that use of the arithmetic mean had a large effect on results based on the NOAEL.

5. Conclusion

Recent studies provide sufficient evidence to support revision of the current Mn RfC. Studies support:

- Use of a BMDL (or BMCL) or a NOAEL study, eliminating the need for a LOAEL UF;
- Use of chronic studies, eliminating the need for a subchronic UF;
- Elimination of a UF to account for lack of developmental data, based on recent animal studies;
- Elimination of a UF for potential differences in the toxicity of different forms of Mn, based on the most likely forms of Mn in the environment.

Therefore, using data from recent epidemiology and toxicology studies leads to an Mn RfC of 2–7 $\mu g/m^3$.

Conflict of interest

One of the authors (Barbara D. Beck) has been named as an expert in litigation involving air exposures to manganese, among other constituents. Some of the underlying work for this manuscript was conducted in the context of an assignment from an industrial client. Preparation of the manuscript was not supported by any client and the opinions are solely those of the authors.

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